INTERNATIONAL SEARCH REPORT

...formation on patent family members

International Application No
PCT/EP 00/01471

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9209589 A	11-06-1992	FR 2669631 A	29-05-1992
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/01471

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D305/14 A61K31/335 C07D413/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 92 09589 A (RHONE-POULENC) 11 June 1992 (1992-06-11) the whole document	1,2

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 May 2000	07/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Francois, J

Form PCT/ISA/210 (second sheet) (July 1992)

02

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SCB 528 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/01471	23/02/2000	02/03/1999
International Patent Classification (IPC) or national classification and IPC C07D305/14		
Applicant INDENA S.P.A.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06/09/2000	24.11.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Schmid, A Telephone No. +49 89 2399 8591

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/01471

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-9 as originally filed

Claims, No.:

1-9 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-9
	No:	Claims
Inventive step (IS)	Yes:	Claims 1-9
	No:	Claims
Industrial applicability (IA)	Yes:	Claims 1-9
	No:	Claims

2. Citations and explanations
see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1) The closest prior art represented by US-A-5,476,954 or WO-A-9209589 discloses a process for the preparation of taxanes (e.g. paclitaxel) starting form 10-deacetylbaccatin III protecting the C-7 hydroxyl with 2,2,2-trichloroethoxycarbonyl (TROC) and the C-10 hydroxyl with TROC or an acetyl group.

The critical step of such a preparation was the selective esterification at C-7 with a group easily and selectively removable. The present problem was to obtain the taxanes in higher yields than the known methods (cf. above and the prior art as discussed on present pages 1 and 2).

The problem could be solved by a process comprising the step of simultaneous protection of the hydroxyl groups at the 7- and 10-positions of 10-deacetylbaccatin III with trichloroacetyl groups which was not disclosed in the prior art (Article 33(2) PCT). In this way surprisingly it was possible to achieve a remarkable improvement in the obtained yields.

Accordingly, the subject-matter of present claims 1-8 does also involve an inventive step and thus meets the requirements of Article 33(3) PCT. However, the applicant is requested to put forward test results with respect to the obtained yields in support of his arguments since this cannot be easily derived from the present examples

2) Present claim 9 is directed to an intermediate of the claimed process which is not disclosed in the prior art (Article 33(2) PCT). Also its usefulness in the above process was not predictable from the prior art and therefore this compounds also fulfils the requirements of Article 33(3) PCT.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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C07D 305/14, A61K 31/335, C07D 413/12

A1

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(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: BOMBARDELLI, Ezio [IT/IT]; Via Val di Sole, 22, I–20141 Milano (IT).

(74) Agents: MINOJA, Fabrizio et al.; Bianchetti Bracco Minoja S.r.l., Via Rossini, 8, I–20122 Milano (IT).

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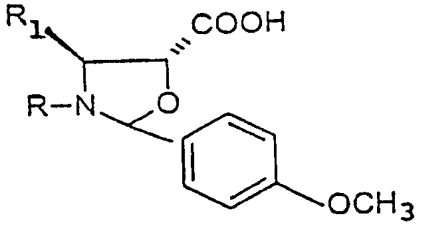
Published
With international search report.

(54) Title: A PROCESS FOR THE PREPARATION OF TAXANES FROM 10–DEACETYLBACCATIN III



(VII)

(57) Abstract

A process for the preparation of taxane derivatives by reacting 10–deacetylbaccatin III protected at the 7– and 10– positions with tricloroacetyl groups, with a compound of formula (VII) subsequent removal of the protective groups and hydrolysis of the oxazolidine ring.

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A PROCESS FOR THE PREPARATION OF TAXANES FROM 10-DEACETYLBACCATIN III

The present invention relates to a process for the preparation of taxanes from 10-deacetylbaccatin III.

Paclitaxel is a known antitumor drug with taxan structure, whose industrial preparation is particularly complex.

Paclitaxel was first isolated by extraction from the trunk barks of *Taxus brevifolia*, and it is at present synthesized starting from 10-deacetylbaccatin III, an intermediate present in the leaves of different species of taxus, particularly in those of *Taxus baccata* L., thereby overcoming the environmental problems connected with the availability of bark of T. brevifolia.

A number of synthetic methods are reported in literature: US Re. 34,277 (reissue of US 4,924,011) discloses the semi-synthesis of Paclitaxel starting from 10-deacetylbaccatin III protected at the C-7 hydroxyl group with a trialkylsilyl group, in particular triethylsilyl, and at the 10- position with an acetyl group. In WO 98/08832, the protection of the C-7 hydroxyl group is carried out using a trichloroacetyl group. The thus protected baccatin III derivative is reacted with acetyl bromide and, subsequently, with the suitable phenylisoserine derivative to obtain Paclitaxel, following deprotection of the hydroxyl groups at 7 and 2' and benzoylation of the amine.

In WO 93/06094, Paclitaxel is prepared by reacting a beta-lactam-type compound with 7-triethylsilyl-baccatin III. The desired product is obtained by deprotection in acid medium.

In US 5 476 954, the synthesis of Paclitaxel is carried out starting from 10-deacetylbaccatin III,

protecting the C-7 hydroxyl with 2,2,2-trichloroethoxycarbonyl (Troc) and the C-10 hydroxyl with Troc or with an acetyl group.

It is therefore evident that the critical step for the synthesis of Paclitaxel is the selective esterification at C-7 with a group easily and selectively removable. Until now, 7-triethylsilyl-deacetylbaccatin III has been considered the key intermediate. The yield reported for the derivatization of 10-deacetylbaccatin III to 7-triethylsilyl-10-deacetylbaccatin III is about 85%, using 5 to 20 mols of silylating agent. The yield of the subsequent acetylation to give 7-triethylsilylbaccatin III is also about 85%.

US 5 621 121 and US 5 637 723 disclose the synthesis of taxanes, including Paclitaxel, by reacting suitably protected baccatin III or 10-deacetylbaccatin III with oxazolidine-5-carboxylic acids bearing at the 2- position a phenyl group substituted with alkoxy groups (US 5 621 121) or with trihaloalkyl groups, in particular trichloromethyl (US 5 637 723), followed by deprotection by opening of the oxazolidine ring.

The protective groups considered particularly suitable comprise silyl, 2,2,2-trichloroethoxycarbonyl or 2-(2(trichloromethyl)propoxy)carbonyl groups.

Substantially the same methods can also be used for the preparation of Docetaxel, another known taxan derivative widely used in clinics.

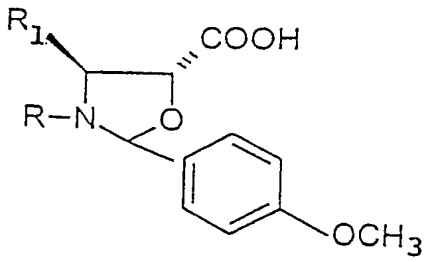
It has now been found a process for the preparation of taxanes, in particular Paclitaxel and Docetaxel, which attains higher yields than the known methods.

The process of the invention, shown in the following Scheme, comprises:

a) simultaneous protection of the hydroxyl groups at the 7- and 10- positions of 10-deacetylbaccatin III with

trichloroacetyl groups.

b) subsequent esterification of the hydroxyl at the 13-position by reaction with a compound of formula (VII):



(VII)

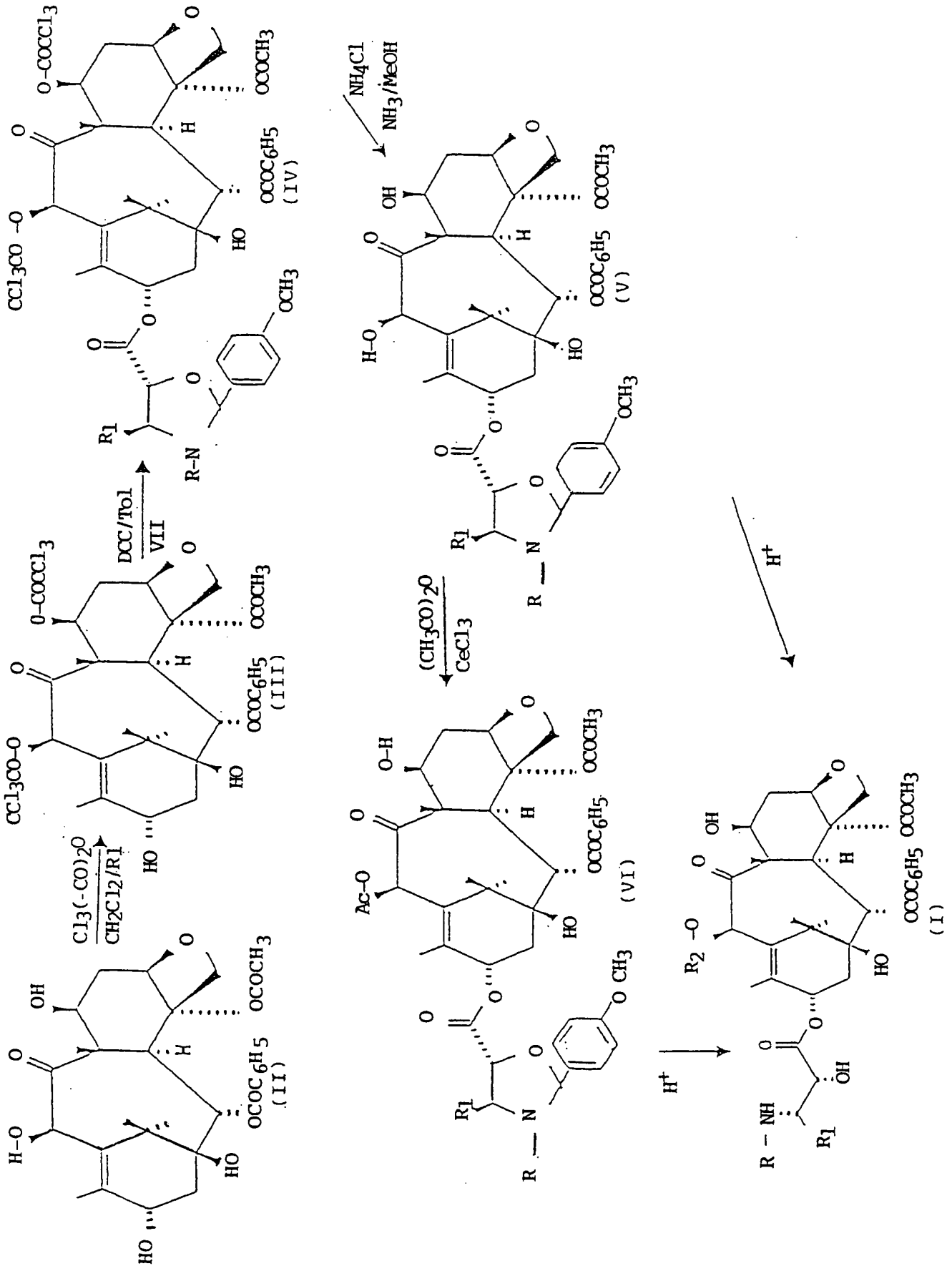
wherein R is tert.butoxycarbonyl, benzoyl or the residue of a straight or branched aliphatic acid and R_1 is phenyl or a straight or branched alkyl or alkenyl;

c) removal of the trichloroacetic protective groups;

d) optional selective acetylation of the hydroxyl at the 10- position, for those compounds in which R_2 is acetyl;

e) acid hydrolysis of the oxazolidine ring.

Scheme


Cl3(-CO)2O
CH2Cl2/R1
DCC/Tol
VII
NH4Cl
NH3/MeOH
(CH3CO)2O
CeCl3
H+
H+

The process of the invention differs from those of the prior art in that the reaction sequence used provides a simpler route than the known processes cited above and a remarkable improvement in the obtained yields.

Step a) is conventionally effected with trichloroacetic anhydride in suitable solvents and in the presence of bases such as pyridine, triethylamine and the like.

The esterification with the oxazolidine-5-carboxylic acid derivative is carried out in the presence of a condensing agent such as dicyclohexylcarbodiimide or other known reagents, in an anhydrous organic solvent, preferably aliphatic, aromatic or chlorinated hydrocarbons, at temperatures ranging from room temperature to the boiling temperature of the solvent.

The resulting oxazolidine ester is then deprotected by removing the 7- and 10- trichloroacetyl groups by treatment with NH_4OH/NH_4Cl in aliphatic alcohols, preferably methanol.

The selective acetylation of the hydroxyl at the 10-position is carried out with acetic anhydride in the presence of cerium III, scandium or ytterbium salts, in a solvent such as tetrahydrofuran, dichloromethane, ethyl acetate, at temperatures ranging from 5 to 40°C.

The treatment with organic or inorganic acids in solvents such as methanol, ethanol, tetrahydrofuran, at temperatures ranging from about -2 to +2°C, yields the desired taxane derivatives. The use of formic acid in tetrahydrofuran at a temperature of 0°C is particularly preferred.

The oxazolidine intermediates are known or can be prepared with known methods, by reaction of an isoserine ester with 4-methoxy-benzaldehyde.

The choice of anisic aldehyde proved to be

particularly important for the formation of the oxazolidine, in that oxazolidine acid, contrary to the methods described in US 5 621 121, 5 637 723 (Rhône-Poulenc Rorer), and in 5 821 363 (UpJohn), can easily be crystallized and adjusted to a 95:5 isomer ratio, which is extremely useful and advantageous for the subsequent step. Furthermore, the oxazolidine carboxylic acid obtainable with anisic aldehyde is particularly stable during the deprotection of the trichloroacetic ester and the subsequent acetylation step. In these conditions, 2,4-dimethoxybenzaldehyde used in US 5 821 363 or chloral or p-trichloromethyl-benzaldehyde as described in US 5 621 121 and 5 637 723 (Rhône-Poulenc Rorer) are not sufficiently stable.

The process of the invention, in addition to Paclitaxel (R = benzoyl, R_1 = phenyl) and Docetaxel (R = tert.butoxycarbonyl, R_1 = phenyl), also provides other taxane derivatives efficiently and conveniently.

The compounds of formula IV have never been described before and are therefore a further object of the invention, as intermediates useful for the synthesis of taxane derivatives.

The following Examples illustrate the invention in greater detail.

Example 1 — Preparation of 7,10-bis-trichloroacetyl-10-deacetylbaccatin III.

A solution of 10 g of 10-deacetylbaccatin III (18.4 mmol) in 125 ml of dry methylene chloride and 42 ml of pyridine is added dropwise with 4.77 ml of trichloroacetic anhydride (42.32 mmol). The reaction mixture is stirred for three hours or anyhow until completion of the reaction, checked by TLC on silica gel using a 5:5 n-hexane/ethyl acetate mixture as eluent. Upon completion of the reaction, 5 ml of methanol are added to destroy the

trichloroacetic anhydride excess, then water. The organic phase is thoroughly washed with HCl (0.1 M solution in water) to remove pyridine, whereas the remaining organic phase is dried over $MgSO_4$ and concentrated to dryness under vacuum. A pale yellow solid (17 g) is obtained, which upon crystallization from chloroform shows the following chemical and spectroscopical characteristics:
IR (KBr) 3517, 1771, 1728, 1240, 981, 819, 787, 675 cm^{-1};
^{1}H-NMR (200 MHz); δ 8.11 (Bz AA'), 7.58 (Bz C), 7.46 (Bz, BB'), 6.50 (s, H-10), 5.72 (m, H-H-2), 5.02 (d, J = 8 Hz, H-5), 4.95 (m, H-13), 4.37 (d, J = 8 Hz, H-20a), 4.18 (d, J = 8 Hz, H-20b), 4.02 (d, J = 6 Hz, H-3), 2.32 (s, 4-Ac), 2.22 (s, H-18), 1.91 (s, H-19), 1.25 and 1.11 (s, H-16, H-17), m.p. = 172-175°C, $[\alpha]_D$-36°(MeOH; C = 0.6).

Example 2 — Preparation of 13-(2-(4-methoxyphenyl)-N-benzoyl-4-phenyl-oxazolidyl-)-10-deacetylbaccatin III.

17 g of 7,10-bistrichloroacetyl-10-deacetylbaccatin III are dissolved in 250 ml of anhydrous toluene and added under stirring with 12.6 g of 2-(4-methoxyphenyl)-N-benzoyl-4-phenyl-oxazolidine-5-carboxylic acid and 6 g of DCC. After stirring overnight at 40°C, the reaction mixture is filtered and concentrated to dryness. The residue is dissolved in 300 ml of methanol/tetrahydrofuran and added with 24 ml of a 2M NH_3 aqueous solution. After 1.5 hours at room temperature the reaction mixture is concentrated to small volume under vacuum, then diluted with water and the whole is extracted with ethyl acetate. The extract is concentrated to dryness and the residue is purified on a silica gel column, eluting the product with a 1:1 ethyl acetate/petroleum ether mixture, to obtain 16.8 g of the title product with m.p. 135°C and $[\alpha]_D$ = -58° (MeOH, C = 0.5).

Example 3 — Preparation of 13-(2-(4-methoxyphenyl)-N-benzoyl-4-phenyl-oxazolidyl)-baccatin III.

A solution of 13.7 g of the product of example II in 200 ml of tetrahydrofuran is added with 56 ml of a 10% suspension of $CeCl_3.7H_2O$ in tetrahydrofuran, followed by 5.5 ml of acetic anhydride. After stirring overnight at room temperature, the reaction mixture is filtered, the filtrate is treated with methanol and concentrated to small volume; the mixture is diluted with H_2O and the product is extracted with ethyl acetate, to obtain 12 g (84%) of 13-(2-(4-methoxybenzilydene)-N-benzoyl-4-phenyl-oxazolidyl-)-baccatin III having the following physical and spectroscopical characteristics:

^{1}H-NMR: 8.07 (d, Bz), 7.60-7.19 (m, aromatic), 7.48 - 6.90 (AA', BB', p-OMePh), 6.33 (s, H-10), 5.67 (d, J = 5 Hz, H-2), 5.56 (br s, H-3'), 4.93 (d, J = 8 Hz, H-5), 4.90 (br s, H-2'), 4.45 (m, H-7), 4.28 (d, J = 8 Hz, H-20a), 4.16 (d, J = 8 Hz, H-20b), 3.82 (s, OMe), 2.27 (s, Ac), 2.08 (s, OAc), 1.66 (s, H-19), 1.29 - 1.16 (s, H-16, H-17), m.p. 146°C, $[\alpha]_D$ = -62° (MeOH, C = 0.8).

Example 4 — Preparation of Paclitaxel

12 g of 13-(2-(4-methoxyphenyl)-N-benzoyl-4-phenyl-oxazolidyl)-baccatine III are dissolved in 50 ml of tetrahydrofuran and added at 0°C with 5 ml of formic acid; the reaction mixture is left under stirring at 0°C for three hours, then diluted with water; formic acid is neutralized with $KHCO_3$ and the suspension is repeatedly extracted with ethyl acetate. The ether-acetic extracts are washed with water and concentrated to small volume. Upon crystallization from the same solvent, 10.5 g of Paclitaxel are obtained having the same chemical-physical and spectroscopical characteristics as described in literature.

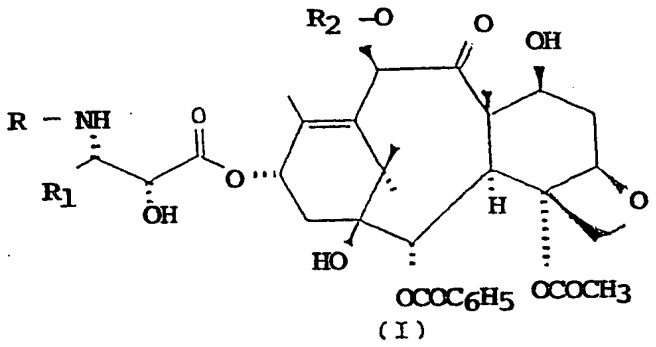
Example 5: Preparation of Docetaxel.

17 g of 7,10-bistrichloroacetyl-10-deacetylbaccatin III are dissolved in 250 ml of anhydrous toluene and added

under stirring with 11.6 g of 2-(4-methoxyphenyl)-N-tert.butoxycarbonyl-4-phenyl-oxazolidine-5-carboxylic acid and 6 g of DCC. After stirring overnight at 40°C, the reaction mixture is filtered and concentrated to dryness. The residue is dissolved in 300 ml of methanol/tetrahydrofuran and added with 24 ml of a 2M NH_3 aqueous solution. After 1.5 hours at room temperature, the reaction mixture is concentrated to small volume under vacuum, then diluted with water and the whole is extracted with ethyl acetate. The extract is concentrated to dryness and 10 g of this residue are dissolved in THF and added at 0°C with 5 ml of formic acid. The reaction mixture is left under stirring at 0°C for three hours, then diluted with water; formic acid is neutralized with $KHCO_3$, the suspension is repeatedly with ethyl acetate. The organic extracts are washed with water and concentrated to small volume. Upon crystallization from the same solvent, 9.2 g of Docetaxel are obtained having the same chemical, physical and spectroscopical characteristics as described in literature.

CLAIMS

1. A process for the preparation of the compounds of formula I



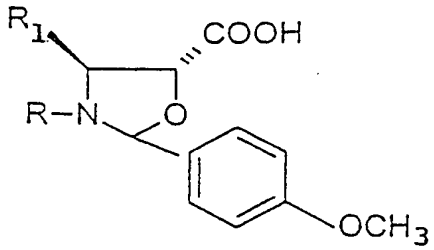
(I)

wherein R is tert.butoxycarbonyl, benzoyl or the residue of a straight or branched aliphatic acid, R_1 is phenyl or a straight or branched alkyl or alkenyl and R_2 is hydrogen or acetyl,

which comprises:

a) simultaneous protection of the hydroxyl groups at the 7- and 10- positions of 10-deacetylbaccatin III with trichloroacetic derivatives;

b) subsequent esterification of the hydroxyl group at the 13- position by reaction with a compound of formula (VII):



(VII)

wherein R is tert.butoxycarbonyl, benzoyl or the residue of a straight or branched aliphatic acid and R_1 is phenyl

or a straight or branched alkyl or alkenyl;

c) removal of the trichloroacetyl protective groups;

d) optional selective acetylation of the hydroxyl group at the 10- position;

e) acid hydrolysis of the oxazolidine ring.

2. A process as claimed in claim 1, in which step b) is effected in the presence of a condensing agent and of a base.

3. A process as claimed in claim 2 in which the condensing agent is dicyclohexylcarbodiimide and the base is pyridine.

4. A process according to any one of the above claims, in which the trichloroacetoxy groups at the 7- and 10-positions are removed by treatment with NH_4OH/NH_4Cl in aliphatic solvents.

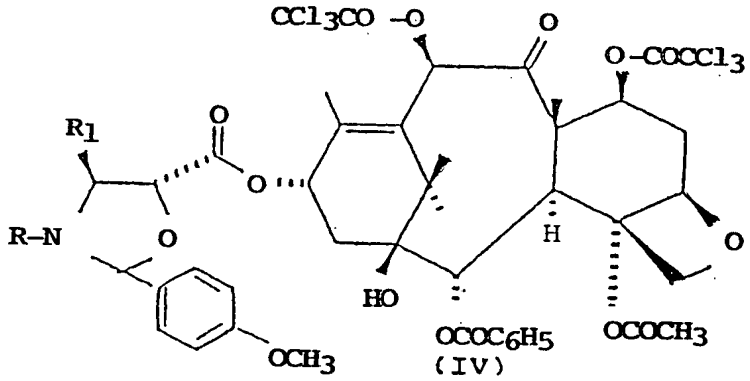
5. A process according to any one of the above claims, in which the selective acetylation of step d) is carried out by reaction with acetic anhydride in the presence of cerium III, scandium or ytterbium salts.

6. A process according to any one of the above claims, in which step e) is effected with organic or inorganic acids in aliphatic alcohols or tetrahydrofuran.

7. A process as claimed in claim 6, in which the hydrolysis is carried out with formic acid.

8. A process according to any one of the above claims, for the preparation of Paclitaxel (R = benzoyl, R_1 = phenyl, R_2 = acetyl) or Docetaxel (R = tert.butoxycarbonyl, R_1 = phenyl, R_2 = H).

9. Intermediates of formula IV



(IV)

wherein R and R_1 are as defined in claim 1.

INTERNATIONAL SEARCH REPORT

Inter[redacted] Application No
PCT/EP 00/01471

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D305/14 A61K31/335 C07D413/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 92 09589 A (RHONE-POULENC) 11 June 1992 (1992-06-11) the whole document	1,2

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 May 2000	07/06/2000

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inter... Application No
PCT/EP 00/01471

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